REMARKS

Upon entry of this amendment, claims 401, 411, 414, 416, 419, 422-424, 437-438, 464-465, 469-471 and 478-480 will be pending in the application. Claims 412, 417, 418, 462, 466, 467, 472-477 and 481 are cancelled herein. Applicants reserve the right to pursue the subject matter of these claims in one or more continuing applications. Claims 401 and 411 are amended herein. Support for these amendments can be found throughout the as-filed specification, for example, at least on page 74, lines 3-11; page 111, lines 1-22 and Example 5 at page 137 -138. No new matter is added.

Rejections Under 35 U.S.C. § 103(a)

Claims 401, 411, 412, 414, 416-419, 422-424, 462, 464-467, and 469-481 are rejected under 35 U.S.C. § 103(a) as being unpatentable over US Patent Publication No. 2002/0159984 to Brown ("Brown") over U.S. Patent No. 6,413,772 to Block ("Block"). Applicants traverse with respect to the pending claims, as amended herein.

Claims 401 and 411 (from which the remaining claims subject to the rejection depend) are amended herein to recite methods for *ex-vivo* expansion of hematopoietic stem cells by culturing the cells under conditions which inhibit differentiation by providing nicotinamide, nicotinamide analog, or nicotinamide derivative in an amount effective to inhibit differentiation, wherein the effective amount to inhibit differentiation is 1.0 mM to 10 mM.

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art.[1] It is also well recognized that a prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention.[2]

Moreover, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one ordinary skill in the art.[3]

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[1] *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988).

[2] *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983).

[3] MPEP §2143.01, citing *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, 82 USPQ2d 1385, 1396 (2007)

Applicants submit that the combination of Brown and Block teaches away from the present invention and that one of ordinary skill in the art would not combine the teachings of Brown and Block to reach the present invention with a predictable results.

For clarity, Applicants are describing the teachings of Brown and Block individually but are traversing the rejection with respect to the combination of these references, *infra*. That is, the Applicants are not attacking the references individually as stated by the Examiner on page 12 of the Final Office Action.

Brown does not teach or suggest using nicotinamide for inhibiting the differentiation of the $CD34^+$stem cells; and most certainly, does not teach or suggest inhibiting the differentiation of the $CD34^+$stem cells by using nicotinamide in the critical range of 1.0 mM to 10 mM, as required by the instant claims. Rather, Brown merely lists nicotinamide, at a concentration of 4 mg/L, along with 44 other compounds, as a component of IMDM. *See*, for example, Brown at Table I, page 4. That is, Brown mentions that nicotinamide is one of a number of "...various vitamins and co-factors, such as riboflavin, nicotinamide, folic acid, choline, biotin, and the like that may be required to sustain cell growth." *See*, for example, Brown at page 3, [0040]. Therefore, at best, the skilled artisan reading Brown, would consider nicotinamide a minor proliferative agent, and would in no way consider nicotinamide an agent required to inhibit differentiation as provided by the instant claims.

Further, as described previously in the record, nicotinamide concentrations of up to 10 times the 4 mg/L nicotinamide disclosed by Brown are ineffective in inhibiting the differentiation of the $CD34^+$stem cells. *See*, December 30, 2008 Peled Declaration. In contrast, as shown in the data accompanying the Peled Declaration, using nicotinamide in the critical range of 1.0 mM to 10 mM, as required by the instant claims inhibited the differentiation of the $CD34^+$stem cells. *See*, December 30, 2008 Peled Declaration at pages 2-4 and at Figure 1.

Moreover, the culture conditions of Brown teach away from the use of nicotinamide to inhibit the differentiation of $CD34^+$stem cells. Specifically, Brown teaches that one of the problems to be solved in the art to improve stem cell engraftment is to prevent the differentiation of $CD34^+$ cells cultured in a serum containing medium. *See*, Brown, at page 1, paragraph [0009]. Brown solves this problem by culturing the cells in a serum-free medium. *See*, Brown, at page 3, paragraphs [0035]-[0041]. These teachings of Brown are in direct contrast to the instant invention wherein the cells require serum, nutrients and cytokines to promote proliferation but also require an effective amount of nicotinamide to inhibit differentiation (1.0 mM to 10 mM).

As such, the skilled artisan would readily recognize Brown teaches away from claimed the invention by teaching that nicotinamide is not useful for inhibiting the differentiation of $CD34^+$stem cells but is merely one of 45 compounds useful for proliferation.

Block does not cure these deficiencies of Brown.

The Examiner contends that it would have been obvious for one of ordinary skill in the art to increase the concentration of exogenously added nicotinamide to the culture medium taught by Brown to provide an improved IMDM formulation, particular because Block clearly discloses, in an unequivocal manner, that exposing a mixed population of hepatocytes to preferably 610 mg/L of nicotinamide (*e.g.*, equivalent to 5 mM) sustained long term proliferation and viability of hepatocytes. *See*, Final Office Action at page 9. Applicants disagree and respectfully submit the Examiner has misconstrued the teachings of Block.

As described in detail *supra*, the skilled artisan reading Brown, as a whole, would readily recognize that only serum-free culture conditions, not nicotinamide concentration, is useful for inhibiting the differentiation of $CD34^+$stem cells and, as such, would certainly not look to optimize the concentration nicotinamide to provide an improved IMDM formulation.

Even assuming arguendo that the skilled artisan would wish to optimize the nicotinamide concentration of Brown (for the reasons set forth above they would not), the skilled artisan would not combine Brown with Block to reach the present invention with predictable results. Firstly, Block is directed to the growth of completely different cells, hepatocytes, not $CD34^+$ hematopoietic stem cells. One of ordinary skill in the art would readily recognize that that the hepatocyte culture conditions described by Block would be unsuitable to the culturing conditions of $CD34^+$ hematopoietic stem cells. In addition, the skilled artisan reading Block, as a whole, would readily determine that Block teaches away from the inhibition of cell differentiation. Rather, the focus of Block is to provide a culture medium (such as HBM) which supports the long term proliferation, differentiation and viability of hepatocytes. That is, Block discloses a medium for culturing cells which promotes and maintains differentiation (the exact opposite of the instant invention). Specifically, Block teaches that the "medium supports sustained clonal growth of primary hepatocytes and heptocyte cell lines ... this medium further allows complete differentiation of metabolic, structural and secretory functions of the cells grown therein." *See*, Block column 3, line 41 - column 4, line 50. Block further discloses that nicotinamide is utilized as a proliferative agent (*see*, Block column 4, lines 45- 50) and for its ability to maintain hepatocyte differentiation. *See*, Block column 8, lines 26-32. In contrast to

Block and Brown, nicotinamide is not utilized in the present invention as a proliferative agent for $CD34^+$ hematopoietic stem cells; but, rather, nicotinamide is utilized as an inhibitor of $CD34^+$ hematopoietic stem cell differentiation.

Based on the foregoing, Applicants submit that both Brown and Block teach away from using nicotinamide for inhibiting the differentiation of the $CD34^+$stem cells as required by the present invention and that one of ordinary skill in the art combining the teachings of Brown and Block would not, and could not, reach the present invention with predictable results.

Moreover, the data presented in the Peled Declaration and the working example provided in the instant specification at Example 5 readily demonstrates that the present invention provides unexpected and superior properties not taught or suggested by the prior art, *e.g.*, that the critical range1.0 mM to 10 mM exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative inhibits differentiation of the CD34+ stem cells, while permitting expansion, *ex vivo*.

Applicants respectfully request reconsideration and withdrawal of the present rejection.

Claims 437, and 438 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Brown and Block and further in view of Banasik *et al.*, 1992 JBC, 1569-1575 ("Banasik"). *See*, Office Action at pages 11-12. Applicants traverse with respect to the pending claims, as amended.

As described above, Brown and Block teach away from the present invention and do not teach or suggest using nicotinamide for inhibiting the differentiation of the $CD34^+$stem cells and do not teach or suggest using the critical range of 1.0 mM to 10 mM, as required by the instant claims.

Banasik does not cure the deficiencies of Brown and Block. In contrast, Banasik merely discloses that benzamide, as well as nicotinamide, is an inhibitor of poly(ADP-ribose) synthetase activity. Banasik is silent with regard to the use of nicotinamide or nicotinamide analogs for inhibition of differentiation of $CD34^+$stem cells.

As such, Applicants submit that the present invention is not obvious in view of the combination of Brown, Block and Banasik. Applicants respectfully request reconsideration and withdrawal of the present rejection.

CONCLUSION

Applicants submit that the application is in condition for allowance and such action is respectfully requested. However, if upon receipt and review of this amendment, the Examiner believes that the present application is not in condition for allowance and that changes can be suggested which would place the claims in allowable form, the Examiner is respectfully requested to call Applicant's undersigned counsel at the number provided below.

Respectfully submitted,

Ivor R. Elrifi, Reg. No. 39,529
Matthew Pavao, Reg. No. 50,572
Attorneys for Applicants
c/o MINTZ, LEVIN
Tel: (617) 542-6000
Fax: (617) 542-2241
Customer No.: 30623

Dated: June 29, 2009

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